Heart muscle disease related to HIV infection: prognostic implications

Peter F Currie, Ashok J Jacob, Angus R Foreman, Robert A Elton, Ray P Brettle, Nicholas A Boon

Abstract

***Objectives*—To determine the natural course of heart muscle disease in patients infected with HIV.**

***Design*—Prospective echocardiographic survey and observational study over four years.**

***Setting*—Edinburgh.**

***Subjects*—296 adults infected with HIV (mean age 32·7 years (range 21·5 to 67·6) drawn from all the major groups at risk of HIV infection in Britain.**

***Main outcome measures*—Detection of myocardial dysfunction and time to death from index echocardiogram in serial echocardiography.**

***Results*—Cardiac dysfunction was identified in 44 subjects (dilated cardiomyopathy, 13; isolated right ventricular dysfunction, 12; borderline left ventricular dysfunction, 19). Dilated cardiomyopathy was strongly associated with a CD4 cell count of $<100\times10^6$/l, in contrast with the other forms of cardiac dysfunction. During the study 12/13 (92%) subjects with dilated cardiomyopathy, 5/12 (42%) with right ventricular dysfunction, and 8/19 (42%) with borderline left ventricular function died of conditions related to AIDS. Survival was significantly reduced in the subjects with dilated cardiomyopathy compared with those with normal hearts ($P<0·001$). The median survival from the index echocardiogram was 101 days (95% confidence interval 42 to 146) for the subjects with cardiomyopathy compared with 472 days (383 to 560) for those with normal hearts and a CD4 cell count of $<20\times10^6$/l. No significant difference existed in survival for subjects with borderline left or isolated right ventricular dysfunction.**

***Conclusion*—Even after adjustment for the significantly reduced CD4 cell count with which dilated cardiomyopathy is associated, the outlook for patients with HIV infection and dilated cardiomyopathy is poor. Isolated right and borderline left ventricular dysfunction are not associated with reduced CD4 cells counts and do not carry adverse prognostic implications.**

Department of Cardiology, Royal Infirmary, Edinburgh EH3 9YW
Peter F Currie, *British Heart Foundation junior research fellow*
Ashok J Jacob, *registrar*
Nicholas A Boon, *consultant cardiologist*

Regional Infectious Disease Unit, City Hospital, Edinburgh EH10 5SB
Angus R Foreman, *data manager*
Ray P Brettle, *consultant physician*

Medical Statistics Unit, University of Edinburgh, Edinburgh EH8 9AG
Robert A Elton, *senior lecturer*

Correspondence to:
Dr P F Currie.

BMJ 1994;309:1605-7

Introduction

The cardiac complications of HIV infection and AIDS are now well documented.[1,2] They include pericardial effusions, disturbances of rhythm, malignant infiltration, marantic endocarditis, and heart muscle disease. With improved clinical surveillance and treatment, more patients are surviving potentially fatal opportunistic infections only to succumb to neoplasia or end organ damage.[3] Heart muscle disease is one such complication and seems destined to become an important cause of cardiac failure worldwide. The natural course of heart muscle disease that is related to HIV infection has not yet been established, largely because most published work has been based on small or cross sectional surveys. Anecdotal evidence exists that patients with pronounced impairment of left ventricular function have a poor prognosis, but this has yet to be confirmed by a formal survival study.[4-6]

A cohort of patients with HIV infection has been studied prospectively in Edinburgh since 1990. Most of the patients attend a single centre, where detailed records are kept. We investigated the natural course of the various forms of heart muscle disease and determined the effect of each condition on survival.

Subjects and methods

Over four years, 296 subjects with HIV infection (mean age 32·7 years (range 21·5 to 67·6)) from all the major groups at risk of HIV infection in Britain (203 injecting drug users, 52 homosexuals, 28 heterosexuals, seven bisexuals, three recipients of blood products, and three patients with multiple risk factors) were assessed with serial echocardiography, chest radiography, and electrocardiography. (One hundred and fifty four patients were reported on previously.[2]) According to criteria from the Centers for Disease Control,[7] AIDS was diagnosed in 100 subjects, 89 subjects were classed as group IV without AIDS and 45 as group III, and 10 subjects had asymptomatic HIV infection. A contemporary classification was not available for 52 subjects.

ECHOCARDIOGRAPHY

We used phantom calibrated ultrasound machines (Sonos 100 and 1000, Hewlett Packard) with 2·5 MHz and 3·5 MHz transducers with subjects in the left lateral position. We obtained left ventricular M mode tracings from long and short axis parasternal views at the level of the mitral valve papillary muscles, and we used on screen callipers to measure end diastolic and systolic dimensions. We calculated the left ventricular fractional shortening as the difference between these two measurements divided by the end diastolic size. The echocardiograms were stored on video tape and were subsequently analysed by the operator and two independent observers blinded to the clinical history of the subjects. M mode measurements were unobtainable in 20 subjects, but cardiac assessment based solely on two dimensional imaging was normal in all these cases.

Patients found to have cardiac dysfunction were grouped into three categories: dilated cardiomyopathy, isolated right ventricular dysfunction, and borderline left ventricular dysfunction (box). None of the subjects with cardiac dysfunction had received anthracycline drugs during the study.

We obtained CD4 cell counts by lymphocyte immunophenotyping using a flow cytometer (FACScan, Becton Dickinson). We obtained information on the clinical status of each subject and, where appropriate, the cause and date of death from hospital records and postmortem reports.

Cardiac dysfunction found in subjects

Dilated cardiomyopathy
A fractional shortening of <28%, with global left ventricular hypokinesia reported by all three observers

Isolated right ventricular dysfunction
Right ventricle larger than left ventricle on standard two dimensional views

Borderline left ventricular dysfunction
Left ventricular end systolic diameter >58 mm but preserved systolic function (fractional shortening >28%) or global left ventricular dysfunction reported by one or two but not all three observers

STATISTICAL METHODS

The primary end point was mortality from a condition related to AIDS, and survival times were censored at death from other causes. Survival curves were obtained with the Kaplan-Meier estimate, and Cox's proportional hazards regression (with BMDP software) was used to compare the three groups with heart muscle disease with the rest of the cohort, who had structurally normal hearts.

The association between CD4 cell counts and cardiac complications was evaluated with a Kruskal-Wallis test to compare the group with normal hearts with the groups with left or right ventricular dysfunction. A Mann-Whitney test was used to compare these three groups with the group with cardiomyopathy.

Results

The mean CD4 cell count of the subjects was 153×10^6/l (range 0-1178) (normal range 500-1400). Over 90% (268/296) of subjects showed evidence of immunosuppression, with a CD4 count of $<400\times10^6$/l, of whom 146 (54%) had a count of $<100\times10^6$/l.

Echocardiographic evidence of cardiac dysfunction was found in 44 subjects (dilated cardiomyopathy in 13, right ventricular dilatation in 12, and borderline left ventricular dysfunction in 19). Chest radiography was less useful, with cardiomegaly (cardiothoracic ratio of >0·5) present in only 46% (6/13) of the patients with dilated cardiomyopathy and in only one patient with isolated left ventricular dysfunction. The electrocardiographic results were unremarkable other than showing non-specific T wave changes, which occurred in all groups.

Symptoms attributable to, and clinical signs of, heart failure were common in the subjects with dilated cardiomyopathy (9/13 (69%)) but were less so in those with borderline left ventricular dysfunction (7/19 (37%)). Breathlessness was common in the subjects with right ventricular dysfunction (6/12 (50%)) but was often attributable to pulmonary disorders.

In all, 123/296 subjects died during the study. Of these, 99 died of conditions related to AIDS and the rest of other causes, including hepatitis (nine) and drug overdose (six). Among those who died of conditions related to AIDS were 12 of the 13 subjects (92%) with dilated cardiomyopathy, 5 of the 12 (42%) with right ventricular dysfunction, and 8 of the 19 (42%) with borderline left ventricular function.

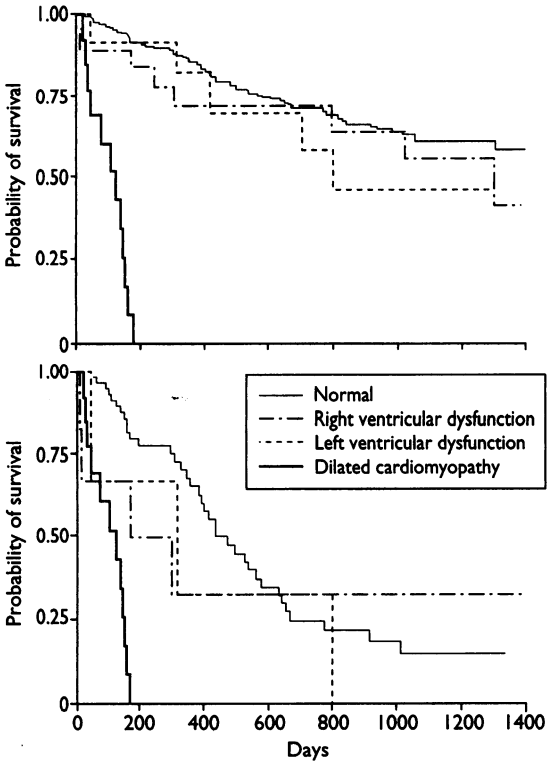
CD4 cell counts were significantly lower ($P<0·001$) in the subjects with dilated cardiomyopathy than in the subjects in the three other groups, but no significant difference ($P=0·27$) occurred between the counts for subjects with isolated right or borderline left ventricular dysfunction and those for the subjects with normal hearts (table). As the patients with dilated cardiomyopathy had more advanced HIV disease (disease lasting from seroconversion to death) Cox's regression was used to correct for the CD4 cell count (and also for age, sex, status according to the criteria from the Centers for Disease Control, interval between echocardiography and the CD4 cell count, and risk group). The figure (top) shows survival curves for deaths related to AIDS for each group. Cox's analysis showed that the subjects with cardiomyopathy had a significantly worse outlook than the patients with normal hearts ($\chi^2=23·43$, $P<0·001$; hazard ratio 11.68 (95% confidence interval 4·32 to 31·58)). The subjects with isolated right and borderline left ventricular dysfunction (with hazard ratios 1·17 (0·51 to 2·70) and 1·48 (0·56 to 3·95) respectively) did not differ significantly from those with structurally normal hearts.

*CD4 cell counts ($\times10^6$/l) in 296 subjects with HIV infection by cardiac status**

Cardiac status	Mean (SD) (range)
Normal	166 (182) (0-1178)
Isolated right ventricular dysfunction	100 (84) (0-240)
Borderline left ventricular dysfunction	107 (117) (0-375)
Dilated cardiomyopathy	7·4 (8) (0-20)

*According to criteria from Centers for Disease Control.

The excess mortality in subjects with cardiomyopathy remained significant at $P<0·001$ even when analysis was restricted to the subjects with CD4 cell counts of $<20\times10^6$/l (figure (bottom)) or when all cause mortality was assessed. Median survival to death related to AIDS was 101 days (95% confidence interval 42 to 146) in those with cardiomyopathy compared with 472 (383 to 560) in 59 of the subjects with normal hearts. Furthermore, the mortality of the 13 subjects with cardiomyopathy was significantly increased when compared with 13 of the patients with normal hearts (median survival 407 days) who were individually matched for age, sex, risk factor for HIV infection, and CD4 cell count ($P<0·01$).



Top: Survival curves for 296 patients who are HIV positive with structurally normal hearts or cardiac dysfunction. Bottom: Survival time to death related to AIDS in 81 subjects with CD4 cell count $<20\times10^6$/l

Discussion

This study confirms previous work that indicated that the prevalence of heart muscle disease in patients with HIV infection is about 15%. Heart muscle disease that is related to HIV infection takes three forms: global left ventricular dysfunction (particularly in late

stage HIV disease), isolated right ventricular dilatation, and borderline left ventricular dysfunction. Cardiac dysfunction is rare in control patients with haematological malignancy[6] and in drug users without HIV infection;[8] it is therefore probably due to a direct effect of HIV infection rather than an effect of the cachexia in patients with AIDS. Little information exists about the natural course of these conditions, although anecdotal reports indicate that dilated cardiomyopathy is associated with a poor prognosis.[4-6]

We have shown that patients with dilated cardiomyopathy generally die early from conditions related to AIDS. This appears to be independent of these patients' CD4 cell count at presentation. Although the statistical power to detect a moderately higher risk is low, the outlook for patients with other forms of heart muscle disease is much less gloomy and may reflect the potentially reversible nature of these conditions. Left ventricular dysfunction may be caused by a self limiting myocarditis that does not progress to overt left ventricular failure. Isolated right ventricular dysfunction may be transient and is possibly related to the pulmonary hypertension associated with parenteral drug use or recurrent bronchopulmonary infection[9] rather than to primary myocardial disease.

Left ventricular failure has rarely been reported as a cause of death in this series, even in patients with cardiomyopathy. We suspect that it was a contributory factor in many cases but may have been overlooked as the features of heart failure are often mistakenly attributed to opportunistic pulmonary infections or anaemia, which are common in patients with HIV infection.[2 6] Similarly, cardiac complications tend to be underdiagnosed even in the face of convincing postmortem evidence.[10]

This study shows that dilated cardiomyopathy is an independent adverse prognostic factor in patients with HIV infection and that it is strongly associated with a very low CD4 cell count. Other conditions with prognostic significance include oral candidiasis,[11 12] hairy leucoplakia,[11 13] severe herpes zoster,[14] and constitutional symptoms,[11] which are all associated with an increased risk of progression from asymptomatic HIV infection to AIDS.

The results of the Concorde trial indicated that it is inappropriate to rely solely on the CD4 cell count when assessing the need for antiretroviral treatment or the long term prognosis of patients with HIV infection.[15] A decline in CD4 cell count correlates well with disease progression in population studies,[11 16 17] but a wide intraindividual variation can exist in both the absolute count and the rate of cell loss over time, reducing the predictive power of this value for individual patients. Decisions on treatment should therefore take into account both the trend of serological results and the clinical factors (including the presence of heart muscle disease).[18]

Key messages

- The cardiac manifestations of AIDS are well recognised and will probably become more common as the treatment of opportunistic infections improves
- Although anecdotal reports suggest that patients with HIV related dilated cardiomyopathy have a poor prognosis, this has not been established in a formal survival study
- This study confirms the prevalence of heart muscle disease related to HIV infection and shows that patients with dilated cardiomyopathy have a poor outlook
- Other recent work has shown that the CD4 cell count cannot alone predict the outcome in patients with AIDS; conditions such as dilated cardiomyopathy will become important prognostic indicators

The cause of heart muscle disease related to HIV infection remains unknown, but many cases seem to be related to an idiopathic lymphocytic myocarditis that is a common postmortem finding in patients with ventricular dysfunction.[1] This may be due to a direct or indirect effect of HIV infection or more rarely, cytomegalovirus infection,[19] but other potential pathogenic factors include nutritional deficiencies, opportunistic infections, and a cardiotoxic effect of antiretroviral drugs.[20] Endomyocardial biopsies and appropriate serological tests for cytomegalovirus or *Toxoplasma gondii*, however, have shown no evidence of opportunistic infection in our patients.[2]

The importance of cardiac involvement in HIV infection should not be ignored. The World Health Organisation has estimated that 38-110 million people worldwide will be HIV positive by the turn of the century. Even if only 4% of these develop dilated cardiomyopathy, HIV will constitute an important cause of heart failure. The outlook for patients with dilated cardiomyopathy is clearly poor and seems to be independent of all other potential prognostic factors. Clinical trials should be set up to evaluate the efficacy of conventional treatment of heart failure in patients with heart muscle disease related to HIV infection.

We thank Mrs Jean Cunningham for her secretarial help in preparing this manuscript. PFC is funded by the British Heart Foundation.

1 Anderson DW, Virmani R. Cardiac pathology of HIV disease. In: Joshi V, ed. *Pathology of AIDS and other manifestations of HIV infection*. New York: Igaku-Shoin, 1992.
2 Jacob AJ, Sutherland GR, Bird AG, Brettle RP, Ludlam CA, McMillan A, *et al.* Myocardial dysfunction in patients infected with HIV: prevalence and risk factors. *Br Heart J* 1992;68:549-5.
3 Peters BS, Beck EJ, Coleman DG, Wadsworth MJH, McGuinness O, Harris JRW, *et al.* Changing disease patterns in patients with AIDS in a referral centre in the United Kingdom: the changing face of AIDS. *BMJ* 1991;302:203-7.
4 Kinney EL, Monsuez JJ, Kiztis M, Vittecoq D. Treatment of AIDS-associated heart disease. *Angiology* 1989;40:970-6.
5 Monsuez JJ, Kinney EL, Vittecoq D, Kitzis M, Rozenbaum W, Francoise d'Agay M, *et al.* Comparison among acquired immune deficiency syndrome patients with and without clinical evidence of cardiac disease. *Am J Cardiol* 1988;62:1311-13.
6 Himelman B, Chung WS, Chernoff DM, Schiller NB, Hollander H. Cardiac manifestations of human immunodeficiency virus infection: a two-dimensional echocardiographic study. *J Am Coll Cardiol* 1989;13:1030-6.
7 Centers for Disease Control: Current trends: classification system for human T lymphotrophic virus type III/lymphadenopathy associated virus infections. *MMWR* 1986;35:334-9.
8 Willoughby SB, Vlahov D, Herskowitz A. Frequency of left ventricular dysfunction and other echocardiographic abnormalities in human immunodeficiency virus seronegative intravenous drug users. *Am J Cardiol* 1993;71: 446-7.
9 Himelman RB, Dohrmann M, Goodman P, Schiller NB, Starksen NF, Warnock M, *et al.* Severe pulmonary hypertension and cor pulmonale in the acquired immunodeficiency syndrome. *Am J Cardiol* 1989;64:1396-9.
10 Acierno LJ. Cardiac complications in acquired immunodeficiency syndrome (AIDS): a review. *J Am Coll Cardiol* 1989;13:1144-54.
11 Moss AR, Bacchetti P, Osmond D, Krampf W, Chaisson RE, Stites D, *et al.* Seropositivity for HIV and the development of AIDS or AIDS related condition: three year follow up of the San Francisco General Hospital cohort. *BMJ* 1988;296:745-50.
12 Klein RS, Harris CA, Small CB, Moll B, Lesser M, Friedland GH. Oral candidiasis in high risk patients as the initial manifestation of the acquired immunodeficiency syndrome. *N Engl J Med* 1984;311:354-8.
13 Greenspan D, Greenspan JS, Hearst NG, Pan LZ, Conant MA, Abrams DI. Relation of oral hairy leukoplakia to infection with the human immunodeficiency virus and the risk of developing AIDS. *J Infect Dis* 1987;155: 475-81.
14 Melbye M, Groossman RJ, Goedert JJ, Eyster ME, Biggar RJ. Risk of AIDS after herpes zoster. *Lancet* 1987;i:728-31.
15 Concorde Coordinating Committee. Concorde: MRC/ANRS randomised double-blind controlled trial of immediate and deferred zidovudine in symptom-free HIV infection. *Lancet* 1994;343:871-81.
16 Goedert JJ, Biggar RJ, Melbye M, Mann DL, Wilson S, Gail MH, *et al.* Effect of T4 count and cofactors on the incidence of AIDS in homosexual men infected with human immunodeficiency virus. *JAMA* 1987;257:331-4.
17 De Wolf F, Lange JMA, Houweling JT, Coutinho RA, Schellekens PT, van der Nordaaj, *et al.* Numbers of CD4+ cells and levels of core antigens of and antibodies to the human immunodeficiency virus as predictors of AIDS among seropositive homosexual men. *J Infect Dis* 1988;158:615-22.
18 Phillips AN, Lee CA, Elford J, Janossy G, Timms A, Bofill M, *et al.* Serial CD4 lymphocyte counts and development of AIDS. *Lancet* 1991;337: 389-92.
19 Herskowitz A, Wu TC, Willoughby S, Vlahov D, Ansari AA, Beschorner WE, *et al.* Myocarditis and cardiotropic viral infection associated with severe left ventricular dysfunction in late stage infection with human immunodeficiency virus. *J Am Coll Cardiol* 1994;24:1025-32.
20 Currie PF, Boon NA. Cardiac involvement in human immunodeficiency virus infection. *Q J Med* 1993;86:751-3.

(Accepted 5 October 1994)